4/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12478442 BIOSIS NO.: 199497499727
High-efficiency gene transfer and high-level expression of wild-type p53 in human lung cancer cells mediated by recombinant adenovirus
AUTHOR: Zhang Wei-Wei (Reprint); Fang Xiangming; Mazur Wojciech; French Brent A; Georges Renee N; Roth Jack A
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JOURNAL: Cancer Gene Therapy 1 (1): p5-13 1994 1994
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A replication-defective and helper-independent recombinant p53 adenovirus was generated. The virus, Ad5CMV-p53, carries an expression cassette that contains human cytomegalovirus E1 promoter, human wild-type p53 cDNA, and SV40 early polyadenylation signal. Four human non-small-cell lung cancer cell lines representing differences in p53 configuration were used to evaluate the Ad5CMV-p53 virus. In the H358 cell line, which has a homozygous deletion of p53, the p53 gene was transferred with 97% to 100% efficiency, as detected by immunohistochemical analysis, when the cells were infected with Ad5CMV-p53 at a multiplicity of infection of 30 to 50 plaque-forming units/cell. Western blots showed that the p53 protein was expressed at a high level. The protein expression peaked at day 3 after infection and lasted for at least 15 days. Growth of the Ad5CMV-p53 virus-infected H358 cells was inhibited 79%, whereas that of noninfected cells or the cells infected with the control virus was not inhibited. Growth of cell line H322, which has a point mutation in p53, was inhibited 72% by Ad5CMV-p53, while that of cell line H460 containing wild-type p53 was less affected (28% inhibition). Tests in nude mice demonstrated that tumorigenicity of the Ad5CMV-p53-treated H358 cells was greatly inhibited. In a mouse model of orthotopic human lung cancer, the tumorigenic H226Br cells, with a point mutation in p53, were inoculated intratracheally 3 days before the virus treatment. Intratracheal instillation of Ad5CMV-p53 prevented tumor formation. These results suggest that adenovirus is an efficient vector for mediating transfer and expression of tumor suppressor genes in human cancer cells and that the Ad5CMV-p53 virus may be further developed into a therapeutic agent for use in cancer gene therapy.

4/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12444051 BIOSIS NO.: 199497465336
In vivo adenoviral-mediated human P53 tumor suppressor gene transfer and expression in rat liver after resection
AUTHOR: Drazan Kenneth E; Shen Xiu Da; Csete Marie E; Zhang Wei Wei; Roth Jack A; Busuttil Ronald W; Shaked Abraham (Reprint)
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JOURNAL: Surgery (St Louis) 116 (2): p197-204 1994 1994
ISSN: 0039-6060
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background. The aim of this study was to establish a clinically

relevant model for gene transfer to liver with an adenoviral vector encoding wild-type p53 as a first step toward use of this class of gene products in the treatment of primary and metastatic liver tumors. Methods. Full-size or 50% hepatectomized rat livers were subjected to asanguineous portal perfusion with a replication-defective adenoviral vector encoding wild-type p53 (Ad5p53), whereas control animals received adenoviral vector encoding Escherichia coli beta-galactosidase (beta-gal) (Ad5LacZ) or Ringer's lactate only. Liver biopsy specimens, blood samples, and liver weight were serially obtained. Gene transfer and expression were confirmed by X-Gal staining for beta-gal, DNA/RNA polymerase chain reaction, (PCR) and Western blots for p53 and -gal. Liver integrity was assessed by histologic findings, serum transaminase levels, and synthetic function. Results. The gene transfer rate in whole liver and after hepatectomy ranged from 20% to 40%. DNA PCR showed Ad sequences in livers transduced with Ad5p53 and Ad5LacZ. RNA PCR and Western blot confirmed expression and production of recombinant wild-type p53. Liver regeneration was not affected by p53 gene transduction. Liver histologic findings- and synthetic function were not different between transduced and control groups. Conclusions. Ad5p53 gene transfer to full-size or hepatectomized livers is efficient. Liver regeneration and hepatocyte function are unaffected by overexpression of p53. Adenovirus-mediated tumor-suppressor transduction of the liver is a safe and promising adjuvant in cancer gene therapy.

4/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12399917 BIOSIS NO.: 199497421202
Induction of chemosensitivity in human lung cancer cells in vivo by adenovirus-mediated transfer of the wild-type p53 gene
AUTHOR: Fujiwara Toshiyoshi; Grimm Elizabeth A; Mukhopadhyay Tapas; Zhang Wei-Wei; Owen-Schaub Laurie B; Roth Jack A
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JOURNAL: Cancer Research 54 (9): p2287-2291 1994 1994
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recombinant adenovirus-mediated transfer of the wild-type p53 gene into monolayer cultures or multicellular tumor spheroids of human non-small cell lung cancer cell line H358, which has a homozygous deletion of p53, markedly increased the cellular sensitivity of these cells to the chemotherapeutic drug cisplatin. Treated cells underwent apoptosis with specific DNA fragmentation. Direct injection of the p53-adenovirus construct into H358 tumors sc. implanted into nu/nu mice, followed by i.p. administration of cisplatin, induced massive apoptotic destruction of the tumors. These results support the clinical application of a regimen combining gene replacement using replication-deficient wild-type p53 adenovirus and DNA-damaging drugs for treatment of human cancer.

4/3,AB/4 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03808403 Genuine Article#: QG730 Number of References: 52
Title: SAFETY EVALUATION OF AD5CMV-P53. IN-VITRO AND IN-VIVO (Abstract Available)

Author(s): ZHANG WW; ALEMANY R; WANG JX; KOCH PE; ORDONEZ NG; ROTH JA
Corporate Source: UNIV TEXAS,MD ANDERSON CANC CTR,DEPT CARDIOVASC& THORAC SURG,THORAC MOLEC ONCOL SECT/HOUSTON//TX/77030; UNIV TEXAS,MD ANDERSON CANC CTR,DEPT PATHOL/HOUSTON//TX/77030; UNIV TEXAS,MD ANDERSON CANC CTR,DEPT TUMOR BIOL/HOUSTON//TX/77030
Journal: HUMAN GENE THERAPY, 1995, V6, N2 (FEB), P155-164
ISSN: 1043-0342
Language: ENGLISH Document Type: ARTICLE
Abstract: In preparation for a clinical trial of the recombinant p53 adenovirus Ad5CMV-p53 for the treatment of lung cancer, the potential adverse effects of Ad5CMV-p53 were assessed in vitro and in vivo. No infectious replication of Ad5CMV-p53 was detectable in HeLa cells infected with extracts from HeLa cells previously Infected with Ad5CMV-p53. No Ad5CMV-p53 DNA replication was detected by (32)Pi labeling in lung cancer cells infected with Ad5CMV-p53 at multiplicities of infection (moi) up to 1,000 pfu/cell (total of 5 x 10(9) pfu viruses). The infectivity and cytotoxicity of Ad5CMV-p53 were examined in vitro in normal human bronchial epithelial (NHBE) cells. At a moi of 50 pfu/cell, Ad5CMV-p53 infection and expression were detectable in 80% of the treated cells. The exogenous p53 protein was first detected by western blotting at 8 hr and peaked at 48 hr after infection. Growth of NHBE cells was not affected by Ad5CMV-p53 infection at a moi of 100 pfu/cell. The pathogenicity of Ad5CMV-p53 was assessed in BALB/c mice. The virus was given to four groups of mice by intratracheal injection at dosages from 10(7) to 10(10) pfu; a fifth group received phosphate-buffered saline alone. None of the viral injections proved to be lethal; Mild to moderate peribronchiolar and perivascular infiltration by mononuclear cells and lymphocytes, with patches of pneumonitis, was the most acute toxic effect detected by histologic analysis in the two high-dose groups. Immunohistochemical analysis of the same paraffin-embedded sections showed that infectivity and level of expression of p53 in lung tissue were dose-dependent. Our results demonstrate that Ad5CMV-p53 is a replication-defective virus that yields a relatively low degree of acute toxicity in mice; these data document a safety profile encouraging for clinical trials of Ad5CMV-p53 in the therapy of lung cancer.

Set	Items	Description
S1	5286	ADENOVIR? (4N) P53
S2	429	S1 NOT PY>1995
S3	189	RD (unique items)
S4	8	S3 (S) (REPLICATION (2N) (DEFECTIVE OR DEFICIENT))

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